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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,884	07/02/2003	Michael Houghton	PP19545.003	6634

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EXAMINER	
CHEN, STACY BROWN	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,884	HOUGHTON, MICHAEL	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,11-14,16-24,41,42,45,47,49 and 59* is/are pending in the application.

4a) Of the above claim(s) *19-21 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,11-14,16-18,22-24,41,42, 45, 49 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed September 16, 2005 is acknowledged and entered. Claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 16-18, 22-24, 41, 42, 45, 49 and 59 are examined. Claims 19-21 and 47 remain withdrawn from consideration, being drawn to a non-elected invention.

Priority

2. The subject matter of claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 16-18, 22-24, 41, 42, 45, 49 and 59 has priority to provisional applications USSN 60/393,694 and 60/394,510, filed July 2, 2002 and July 8, 2002, respectively. The benefit of priority to USSN 09/721,479 and USSN 60/167,502, filed November 22, 2000 and November 24, 1999, respectively, is denied. The subject matter of the instant claims is drawn to a fusion protein comprising a modified NS3 polypeptide having an amino acid substitution that renders the protease of the fusion protein non-functional. The specification of USSN 09/721,479 contemplates a deletion of substitution in the NS3 region in order to render the protease non-functional, but does not teach "at least one amino acid substitution". Therefore, the earliest date to which Applicant may claim priority is July 2, 2002.

3. The following objections and rejections are either withdrawn or moot:

- The objection to the specification for failing to comply with the sequence rules is withdrawn in view of Applicant's amendment to the specification.
- The objection to claim 12 because of a minor grammar error is withdrawn in view of Applicant's amendment.

- The rejection of claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 17, 18 and 22-24 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of Applicant's amendments.
- The rejection of claim 15 under 35 U.S.C. 102(b) as being anticipated by Grakoui *et al.* (*J. Virology*, May 1993, 67(5):2832-2843, "Grakoui") is moot in view of the cancellation of claim 15.

Claim Rejections - 35 USC § 112

4. Claims 1-4, 11, 12, 16, 22 and 59 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a fusion protein consisting of two polypeptides. The new limitation in claim 1, "wherein the fusion protein comprises sequences that are not in the order in which they occur naturally in the HCV polyprotein", is unclear. The closed language of the preamble indicates that the fusion protein is made up only of the modified NS3 polypeptide and the non-NS3 polypeptide. The new limitation indicates that there are possibly other sequences in the fusion protein. Clarification and correction are required to overcome this rejection.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 16-18, 22-24, 41, 42, 45, 49 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paliard *et al.* (WO 01/30812 A2, "Paliard") in view of Houghton *et al.* (US 5,371,017, "Houghton") and Grakoui. The claims are drawn to an immunogenic fusion protein consisting of:

(a) a modified NS3 polypeptide comprising at least one amino acid substitution to the HCV NS3 region, such that protease activity is inhibited, and

(b) at least one polypeptide from a region of the HCV polyprotein other than the NS3 region, wherein the fusion protein comprises sequences that are not in the order in which they occur naturally in the HCV polyprotein.

The modified NS3 polypeptide comprises a substitution of an amino acid corresponding to His-1083, Asp-1105 and/or Ser-1165, numbered relative to the full-length HCV-1 polyprotein. The fusion protein additionally comprises an NS4 polypeptide, an NS5a polypeptide, an NS5b polypeptide, and optionally a core polypeptide. The modified NS3 polypeptide and the other polypeptide are from the same HCV isolate, or from different isolates. The order of the proteins in the fusion protein from amino to carboxy terminal is: modified NS3 polypeptide, NS4 and NS5a. Another order is modified NS3 polypeptide, NS4, NS5a and NS5b. Another combination is modified NS3 polypeptide, NS4, NS5a and optionally, core polypeptide. Another combination is modified NS3 polypeptide, NS4, NS5a, NS5b and optionally, core polypeptide. Also claimed are compositions comprising the fusion proteins described, in combination with a pharmaceutically acceptable excipient. Also claimed are methods of producing a composition

comprising combining the immunogenic fusion protein with a pharmaceutically acceptable excipient. Claims 41, 42, 45 and 49 are drawn to compositions that optionally are comprised of core polypeptide, wherein the core polypeptide comprises the sequence of amino acid depicted at amino acid position 1772-1892 of SEQ ID NO: 6.

Paliard discloses a method for activating HCV-specific T cells using fusion proteins comprising from two to ten or more polypeptides: HCV NS3, NS4, NS5a, NS5b and core polypeptides (abstract and page 17, lines 22-25). The core region of the HCV polyprotein occurs at amino acid positions 1-191 of HCV polyprotein numbered relative to HCV-1. **The order of NS3, NS4, NS5a and NS5b occurs in any order in the fusion protein, as well as polypeptides from HCV various strains (page 16, 16-20, and page 17, lines 7-21).** Paliard also discloses the use of the fusion proteins in compositions that additionally comprise pharmaceutically acceptable carriers (page 22-23, bridging paragraph). Paliard fails to teach an amino acid substitution(s) in the NS3 polypeptide rendering the protease (NS3) inhibited. Paliard further fails to teach the specific substitutions.

However, Houghton teaches that the replacement of critical residue, serine, in the active site of the NS3 (protease) does not significantly alter the structure of the protease, and thus preserves binding specificity. Houghton teaches that the substituted protease retains its recognition and binding properties while failing to effect cleavage of the polyprotein (col. 3, lines 29-34, and col. 14, lines 32-48). With regard to the specific substitution, Grakoui discloses the substitution of alanine for His-1083, Asp-1107 and Ser-1165 in HCV NS3, resulting in uncleaved NS domains. This activity qualifies as inhibited protease activity (abstract). While

the substitution of alanine for Asp-1107 is not Asp-1105 (as claimed), position 1107 corresponds to the HCV-1 polyprotein, thus meeting the limitation of the claim.

It would have been obvious to incorporate Houghton's teachings and Grakoui's teachings into the fusion protein of Paliard. One would have been motivated to render the protease (NS3) non-functional in order to avoid cleavage of polyprotein, as taught by Houghton (col. 3, lines 29-34, and col. 14, lines 32-48). One would have been motivated to substitute the amino acids taught by Grakoui because Houghton discloses that certain substitutions result in the inhibition or ablation of protease function. One would have had a reasonable expectation that Paliard's fusion protein would have worked with Houghton's NS3 amino acid substitution and Grakoui's substitution, because Grakoui demonstrates that the substitutions result in inhibited or non-existent protease activity. Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time of the invention.

6. Applicant's arguments have been carefully considered but fail to persuade. Applicant asserts that the examiner has used improper hindsight to reject the claims. In response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant argues against each of the references individually:

- Applicant asserts that Grakoui fails to teach a HCV fusion protein having sequences that are not in the order in which they occur naturally in the HCV polyprotein.
- Applicant asserts that Houghton fails to teach a HCV fusion protein comprising a modified NS3 polypeptide fused to another HCV sequence.
- Applicant asserts that Paliard fails to teach a HCV fusion protein having an NS3 polypeptide modified such that protease activity is inhibited.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). While the assertions are true, the elements of the invention are present and the motivation to combine the references is present (see above rejection).

Applicant asserts that references fail to teach a HCV fusion protein having sequences that are not in the order in which they occur naturally in the HCV polyprotein. In response to this argument, Paliard teaches that the order of NS3, NS4, NS5a and NS5b occurs in any order in the fusion protein, as well as polypeptides from HCV various strains (page 16, 16-20, and page 17, lines 7-21). Applicant has not addressed this teaching of Paliard which was pointed in the rejection (see above rejection). Taken together with the other references, the invention as a whole remains obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

7. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen

Stacy B. Chen
November 23, 2005